REMARKS

I. Formal Matters

Applicants note that the Examiner has indicated that claim 23 is directed to an invention that is independent or distinct from the invention originally claimed and has withdrawn this claim from consideration.

The Examiner has indicated that blank lines do not separate all the paragraphs of the specification. As this may cause problems with printing, the Examiner has suggested that we submit a substitute specification. Applicants thank the Examiner for this suggestion and respectfully ask that submission of the substitute specification be held in abeyance until the Office has indicated that the claims are allowable.

II. Rejections under 35 U.S.C. § 112, ¶ 1:

Written Description

Claims 1, 2, 4, 11, 13, 14, 16, 21, 22 and 24 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed. (Office Action at page 4.) In particular, the Examiner contends that the specification does not describe, within the full scope of the claims, DNA molecules that encode a

fusion protein comprising two anti-pathogenic proteins joined by a linker peptide. Applicants respectfully traverse this rejection.

The Examiner indicates that the Applicant's previous arguments are not found persuasive because:

(i) linker peptides other than SEQ ID NOs: 1, 2 and 11 are not described;

(ii) the structural features of anti-pathogenic proteins are not described; and

(iii) the features that distinguish proteins and protein domains that are anti-pathogenic from those which are not are not described.

With respect to reason (1), Applicants direct the Examiner's attention to the description from the bottom of page 7 to the bottom of page 9. This section discusses the structure of natural linker peptides and goes on to detail the amino acid residues that are preferred for designing linker peptides to be used in the present invention. In addition, a number of linkers that have been previously identified are discussed (SEQ ID NOs: 12, 13 and 14) before the description moves on to disclose the linkers that are presently claimed in claims 9, 10 and 11. Thus, the Applicants respectfully submit that Examiner is not correct in indicating that other linker peptides are not described. In addition, the discussion of the properties of the amino acids to be used would give the skilled person the ability to design further linker peptides for use in the invention.

In response to reason (ii), i.e., the Examiner's assertion that that the structural features of anti-pathogenic proteins are not described, Applicants respectfully submit

that the specification provides guidance in this regard. The list of preferred proteins on page 6, and the list of proteins preferred for use in making plant resistant to nematodes on page 7, provide information as they list classes of anti-pathogenic proteins: within these classes there are structurally conserved motifs – the names of these classes of proteins would therefore imply particular structural features to the skilled person.

With respect to reason (iii), i.e., the Examiner's assertion that the specification does not describe features that distinguish proteins and proteins domains that are anti-pathogenic from those which are not, Applicants submit that the skilled artisan, using the teachings of the specification as a guide, coupled with what is known in the art, would be able to discern which proteins and protein domains are anti-pathogenic and which are not.

Enablement

The Examiner rejected claims 1-2, 4-11, 13-14, 16, 21-22 and 24, alleging that the specification is not enabled for a method of improving the resistance of a plant to any pathogen by transformation with any DNA construct encoding any two anti-pathogenic proteins joined by a linker peptide of any size. (Office Action at page 5.) Applicants respectfully traverse.

Firstly, Applicants submit that the claims are directed to improving resistance of a plant to nematodes, by using a construct wherein at least one of the two protein domains has proteinase inhibitor activity.

The Examiner's specific objections are:

(i) that not all proteins are small enough to be ingested by nematodes;

(ii) that proteinase inhibitors do not provide resistance to all pathogens, including bacteria;

(iii) that the specification fails to teach the appropriate cellular targeting of the fusion protein;

(iv) that the specification fails to provide any guidance for the use of linkers of any size or sequence in the constructs;

(v) that the specification fails to provide guidance for which anti-pathogenic proteins or protein domains would provide resistance or tolerance to nematodes.

The Examiner indicates that not all proteins are small enough to be ingested by nematodes and cites Urwin et al. for reportedly teaching that a 28kDa green fluorescent protein was too large to be ingested by *Heterodera schachtii*. As Applicants pointed out in the previous response, the skilled artisan would recognize that different nematodes may have different size constraints with respect to ingestion of proteins. That some proteins may not be small enough for ingestion is not determinative of whether the instant specification enables the claimed invention. The claimed invention is directed to those proteins that are ingestible by nematodes. It is axiomatic that a claim is permitted to encompass some inoperative embodiments.

Applicants respectfully submit that given that claim 1 relates to plants resistant to nematodes, assertion (ii) is not relevant.

With respect to assertion (iii), Applicants reiterate that (Gleddie *et al.* 2000) merely speculates that protease inhibitors should be translocated to the appropriate cellular location.

With respect to assertion (iv), as detailed above, the specification does provide information on linkers that can be used in the present invention, detailing particular amino acids that have useful properties and also disclosing 6 different linker peptides that may be of use.

In response to assertion (v), the Examiner is referred to page 7, where a list of nematode genera is given along with the types of anti-pathogenic proteins that are of interest in respect of control of these species. Thus, it is submitted that the specification does provide guidance to the skilled man as to what proteins or protein domains would provide resistance or tolerance to nematodes

Reconsideration and withdrawal of these rejections is therefore respectfully requested.

III. Rejection under § 112(¶2):

The Examiner has rejected claims 1-2, 4-11 and 18-20 for allegedly lacking agreement with the preamble and the positive method steps. (Office Action at page 8.) Solely to expedite prosecution and without acquiescing to the rejection, Applicants have amended the relevant independent claim to ensure that the relevant claims are circular, as suggested by the Examiner.

In addition, the Examiner has indicated that it is unclear whether the phrase '*with anti-pathogenic activity*' in parts (a) and (c) of claims 1 and 13 is intended to modify both '*protein*' and '*protein domain*' or just one of them. (Office Action at page 9.) Solely to expedite prosecution and without acquiescing to the rejection, Applicants have amended the claims to ensure clarity.

Reconsideration and withdrawal of these rejections is therefore respectfully requested.

IV. Rejections Under § 102:

§ 102(b)): Anderson *et al.* (WO 94/13810) and § 102(b) US 6,031,087

The Examiner has maintained the rejection to claims 1-2, 7, 13-14 and 16 as allegedly anticipated under § 102(b) and § 102(e). For the § 102(b) rejection, the Examiner states that Applicant's previous argument has not been found persuasive because '*the domains themselves act as linkers*'. (Office Action at page 10.) Applicants respectfully traverse.

The skilled person would not view the domains of the type II serine protease inhibitor as linkers, but as functional domains of the protein itself. As indicated in the present application, the function of the linker peptide is to join the anti-pathogenic proteins or protein domains without disturbing their function. These domains are not merely joining two further domains together – they are functional domains in their own right.

Moreover, while WO 94/13810 and US 6,031,087 are concerned with plant pathogens, nematodes, and hence, a method of improving nematode resistance in plants,

are not specifically mentioned. Hence the documents do not anticipate the claimed invention. Reconsideration and withdrawal of these rejections is therefore respectfully requested.

102(b): Atkinson *et al.* (WO 96/16173)

The Examiner has maintained the rejection to claims 13 and 21 under 35 U.S.C. § 102(b) as allegedly anticipated by Anderson et al. (WO 96/16173), stating that the Applicants' previous argument has not been found persuasive because '*the hybrid constructs produced by Atkinson* et al. *consist of different fragments of different lengths of cystatin and oryzacystatin are joined*' and '*the constructs thus encode anti-pathogenic domains joined by what are effectively linker domains*'. (Office Action at page 11.)

Applicants respectfully disagree with the Examiner's rejection and submits that the skilled person would not view the fragments of the hybrid proteins as linkers, but as functional fragments of the particular proteins used to make the hybrid. As indicated in the present application, the function of the linker peptide is to join the anti-pathogenic proteins or protein domains without disturbing their function. These fragments are not joining two different proteins domains together – they are part of these protein domains. The skilled artisan would not view this document in the way the Examiner has represented it and would not reasonably believe that it clearly and unambiguously discloses a DNA molecule encoding two proteins, or protein domains, joined by a linker peptide. Reconsideration and withdrawal of these rejections is therefore respectfully requested.

V. Rejections Under § 103

Atkinson et al. (WO 96/16173) in view of Lilley et al.

The Examiner has rejected claims 1-2, 4, 5, 7, 8, 13, 14 16, 21 and 22 as allegedly unpatentable over Atkinson et al. in view of Lilley et al. (Office Action at page 12.) Applicants respectfully traverse.

This rejection under § 103 is based on the contention that Atkinson *et al.* discloses hybrid constructs that encode anti-pathogenic domains joined by what are, in effect, linker domains. The Examiner suggests that it would have been obvious to one skilled in the art to modify the teaching of Atkinson *et al.* by using the disclosure in Lilley *et al.* of the CpTI gene. In particular, the Examiner indicates that the motivation for this comes from page 422, left column, paragraph 2, of Lilley *et al.* where it is stated that cleavage of certain protease substrates by nematode gut extracts can only be inhibited by a combination of both Oc-IΔD86 and CpTI and then from page 423, left column, paragraph 1 where it is suggested that expression of both cysteine and serine proteinase inhibitors in plant roots may enhance the efficiency of nematode control.

Applicants respectfully disagree, in particular, with the Examiner's representation of Atkinson *et al.*, as detailed above. Atkinson *et al.* does not disclose two proteins joined by linker peptides and even if, assuming *arguendo*, it were considered obvious to combine the two documents, no-where is it taught or suggested that the proteins should be expressed as a fusion proteins in plants in which the two domains are joined by a linker peptide. Indeed, the skilled artisan would appreciate that there are a number of ways in which two proteins can be expressed in plants: for

example, by transformation of the plants with two constructs or a single construct comprising more than one expression cassette, or by transformation of two separate plants with one of the constructs and then hybridisation of the resultant plants. As neither Atkinson *et al.* nor Lilley *et al.* discloses or even suggests that the proteins should be expressed in plants as fusion proteins joined by linker peptides, the present invention cannot be considered obvious over the combination of documents.

Atkinson et al. (WO 96/16173) in view of Hepher et al. (EP 0 502 730) and Conkling et al. (US 5,837,867)

The Examiner has rejected claims 1, 2, 4-8, 13, 14, 16, 21, and 22 under 35 U.S.C. 103 for allegedly being obvious over Atkinson et al. in view of Hepher et al and Conkling et al. (Office Action at page 13.) Applicants respectfully traverse.

The Examiner starts from a similar position to that above for this second §103 rejection, indicating that Atkinson *et al.* discloses fusion proteins joined by linkers. Again, Applicants dispute this, for the reason set forth above.

With regard to the combination of Hepher *et al.* and Conkling *et al.* with Atkinson *et al.*, Applicants submit that it appears as though the Examiner is using an impermissible hindsight in levying this rejection. The documents that the Examiner has cited merely provide a list of possible proteinase inhibitors and a possible promoter for expression in roots. No-where is it disclosed or even suggested in Hepher *et al.* that the inhibitors can or should be expressed in combination and, in particular, that they should be expressed as fusion proteins joined by linkers. While it is possible that the skilled

aritsan could have used the proteinase inhibitors of Hepher *et al.* to make fusion proteins, there is nothing in Hepher *et al.* to suggest doing so.

In addition, and importantly, a combination of Atkinson *et al.* and Hepher *et al.* does not result in the presently claimed invention as no-where is it disclosed or even suggested that the proteinase inhibitors can be joined by linkers. In addition, and in *arguendo*, even if it were supposed that Atkinson *et al.* did disclose proteins or protein domains joined by linkers, then there is still nothing in the cited documents to motivate the skilled person to use the proteinase inhibitors of Hepher *et al.* in the constructs of Atkinson *et al.*.

In respect of the disclosure of Conkling *et al.*, it is submitted that this document could only ever be relevant for the subject matter of claim 6, which is concerned with the use of a promoter capable of driving expression preferentially in plant roots. A combination of Atkinson *et al.*, Hepher *et al.* and Conkling *et al.* does not add anything to Atkinson *et al.* and Hepher *et al.* in respect of the other claims. The deficiencies of the Atkinson et al. and Hepher et al. have been highlighted above. Conkling fails to remedy these deficiencies. Hence, the references, considered alone or in combination fail to render the claimed invention obvious.

Reconsideration and withdrawal of the rejections is therefore respectfully requested.

CONCLUSION

Pursuant to the foregoing remarks, Applicants respectfully submit that all of the pending claims fully comply with 35 U.S.C. § 112 and are allowable over the prior art of record. No new matter is added by this amendment. Reconsideration of the application and allowance of all pending claims is earnestly solicited. Should the Examiner wish to discuss any of the above in greater detail or deem that further amendments should be made to improve the form of the claims, then the Examiner is invited to telephone the undersigned at the Examiner's convenience.

Entry of the amendments is respectfully requested.

If there are any additional fees necessary to maintain pendency of this application, then the Office is hereby authorized to charge Deposit Account No. 50-1744 in the name of Syngenta Biotechnology, Inc. for payment of such fees.

Respectfully submitted,

Marcia R. Morton
Attorney for Applicants
Registration No. 46,942

Syngenta Biotechnology, Inc.
Intellectual Property and Licensing
3054 Cornwallis Road
Research Triangle Park, NC 27709-2257
Tel.: 919-541-8566

Date: July 25, 2003